CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074467

Trade Name : RANITIDINE TABLETS USP (PRESENT AS THE HYDROCHLORIDE)

Generic Name: Ranitidine Tablets USP (present as the hydrochloride)

Sponsor :Geneva Pharmaceuticals, Inc.

Approval Date: August 29, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074467

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074467

APPROVAL LETTER

ANDA 74-467

AUG 29 1997

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W. Midway Blvd.
P.O. Box 466
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 16, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ranitidine Tablets USP, 150 mg and 300 mg (present as the hydrochloride).

Reference is also made to your amendments dated March 13, April 24, August 27, and August 28, 1997.

The listed drug product referenced in your application is subject to a period of patent protection which expires June 4, 2002, (patent 4,521,431). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of ranitidine hydrochloride will not infringe on the patent or that the patent is otherwise invalid. You further informed the Agency that Glaxo, Inc. initiated a patent infringement suit against you in the United States District Court for the District of New Jersey (Glaxo Inc., Glaxo Group Limited, and Allen & Hanburys Limited v. Geneva Pharmaceuticals Inc., Ciba-Geigy Corporation, Interchem Trading Corporation and Union Quimico Farmaceutica S.A., Civil Action Nos. 94-1921 and 94-4589.) You also have notified the Agency that the case was dismissed with prejudice on August 6, 1997.

The Agency also recognizes that the 30-month period identified in Section 505(j)(4)(B)(iii) of the Act, during which time FDA was precluded from approving your application, expired prior to the August 6, 1997 decision of the court.

The Agency has reviewed the application of the 180-day exclusivity provisions of the Act in reference to the ANDAs submitted for ranitidine hydrochloride tablets, and has concluded that Genpharm, Inc., as the first ANDA applicant to submit a

Paragraph IV Certification to the patent listed for the referenced drug, received the right to the 180-days of exclusivity. This period of exclusivity expires on August 29, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ranitidine Tablets USP, 150 mg and 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zantac Tablets, 150 mg and 300 mg, respectively, of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

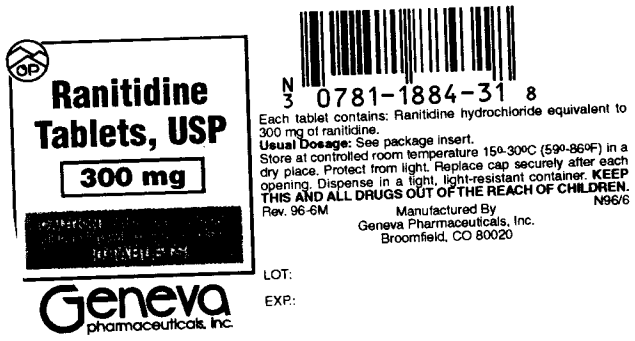
Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074467

FINAL PRINTED LABELING



N 3 0781-1884-31 8

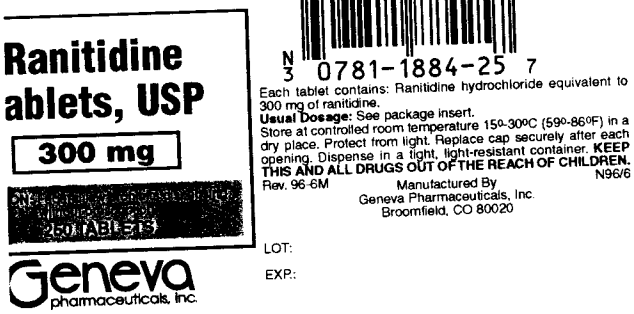
Each tablet contains: Ranitidine hydrochloride equivalent to 300 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 96-6M N96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP:

29 1997



N 3 0781-1884-25 7

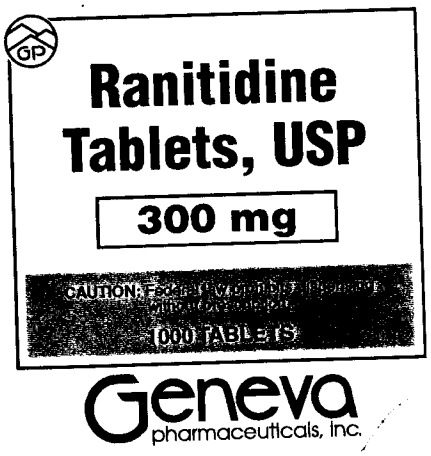
Each tablet contains: Ranitidine hydrochloride equivalent to 300 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 96-6M N96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP:

1997



N 3 0781-1884-10 3

Each tablet contains: Ranitidine hydrochloride equivalent to 300 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 96-6M C96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

104 b

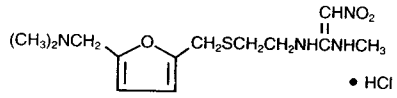
7162

RANITIDINE TABLETS, USP

7162-6

DESCRIPTION: Ranitidine hydrochloride is a histamine H_2-receptor antagonist. Chemically it is *N*-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-*N'*-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

Ranitidine HCl is a white to pale yellow, crystalline substance that is very soluble in water. It has a slightly bitter taste and sulfur-like odor. It has the following structural formula:



$C_{13}H_{22}N_4O_3S \bullet HCl$ M.W. 350.87

Each tablet, for oral administration contains 168 mg or 336 mg ranitidine hydrochloride equivalent to 150 mg and 300 mg ranitidine, respectively. Inactive ingredients: D & C Red #30 Aluminum Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The **300 mg** also contains: D & C Yellow #10 Aluminum Lake.

CLINICAL PHARMACOLOGY: Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine does not lower serum Ca^{++} in hypercalcemic states. Ranitidine is not an anticholinergic agent.

Antisecretory Activity:

1. *Effects on Acid Secretion:* Ranitidine inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in the following table:

Effect of Oral Ranitidine on Gastric Acid Secretion

	Time after Dose, h	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal-, nocturnal-, and betazole-stimulated secretions are most sensitive to inhibition by ranitidine, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

2. *Effects on Other Gastrointestinal Secretions:*

Pepsin: Oral ranitidine does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Oral ranitidine has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: Ranitidine has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions:

a. Gastric bacterial flora — increase in nitrate-reducing organisms, significance not known.

b. Prolactin levels — no effect in recommended oral or IV dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.

c. Other pituitary hormones — no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

d. No change in cortisol, aldosterone, androgen, or estrogen levels.

e. No antiandrogenic action.

f. No effect on count, motility, or morphology of sperm.

Pharmacokinetics: Ranitidine is 50% absorbed after oral administration, compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring at 2 to 3 hours after a 150 mg dose. The elimination half-life is 2.5 to 3 hours.

Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of ranitidine.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL/min, indicating active tubular excretion. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

In man, the N-oxide is the principal metabolite in the urine; however, this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Active Duodenal Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*	Placebo*

2

(creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

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Clinical Trials:

Active Duodenal Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	195	69/182 (38%)†	188	31/164 (19%)
Week 4		137/187 (73%)†		76/168 (45%)

*All patients were permitted p.r.n. antacids for relief of pain.
†$p < 0.0001$.

In these studies patients treated with ranitidine reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

Mean Daily Doses of Antacid

	Ulcer Healed	Ulcer Not Healed
Ranitidine	0.06	0.71
Placebo	0.71	1.43

Foreign studies have shown that patients heal equally well with 150 mg b.i.d. and 300 mg h.s. (85% versus 84%, respectively) during a usual 4-week course of therapy. If patients require extended therapy of 8 weeks, the healing rate may be higher for 150 mg b.i.d. as compared to 300 mg h.s. (92% versus 87%, respectively).

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates.

Maintenance Therapy in Duodenal Ulcer: Ranitidine has been found to be effective as maintenance therapy for patients following healing of acute duodenal ulcers. In two independent, double-blind, multicenter, controlled trials, the number of duodenal ulcers observed was significantly less in patients treated with ranitidine (150 mg h.s.) than in patients treated with placebo over a 12-month period.

Duodenal Ulcer Prevalence

Double-blind, Multicenter, Placebo-controlled Trials					
Multicenter Trial	Drug	Duodenal Ulcer Prevalence			No. of Patients
		0-4 Months	0-8 Months	0-12 Months	
USA	RAN	20%*	24%*	35%*	138
	PLC	44%	54%	59%	139
Foreign	RAN	12%*	21%*	28%*	174
	PLC	56%	64%	68%	165

% = Life-table estimate.
* = $p<0.05$ (Ranitidine versus comparator).
RAN = ranitidine.
PLC = placebo.

As with other H_2-antagonists, the factors responsible for the significant reduction in the prevalence of duodenal ulcers include prevention of recurrence of ulcers, more rapid healing of ulcers that may occur during maintenance therapy, or both.

Gastric Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed gastric ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2		16/83 (19%)		10/83 (12%)
Week 6	92	50/73 (68%)†	94	35/69 (51%)

* All patients were permitted p.r.n. antacids for relief of pain.
† $p = 0.009$.

In this multicenter trial, significantly more patients treated with ranitidine became pain-free during therapy.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): Ranitidine inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison syndrome, systemic mastocytosis, and other pathological hypersecretory conditions (e.g., postoperative, "short-gut" syndrome, idiopathic). Use of ranitidine was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

Gastroesophageal Reflux Disease (GERD): In two multicenter, double-blind, placebo-controlled, 6-week trials performed in the United States and Europe, ranitidine 150 mg b.i.d. was more effective than placebo for the relief of heartburn and other symptoms associated with GERD. Ranitidine-treated patients consumed significantly less antacid than did placebo-treated patients.

The US trial indicated that ranitidine 150 mg b.i.d. significantly reduced the frequency of heartburn attacks and severity of heartburn pain within 1 to 2 weeks after starting therapy. The improvement was maintained throughout the 6-week trial period. Moreover, patient response rates demonstrated that the effect of heartburn extends through both the day and night time periods.

In two additional U.S. multicenter, double-blind, placebo-controlled, 2-week trials, ranitidine 150 mg b.i.d. was shown to provide relief of heartburn pain within 24 hours of initiating therapy and a reduction in the frequency and severity of heartburn.

(See Reverse)

Erosive Esophagitis: In two multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ranitidine 150 mg q.i.d. was significantly more effective than placebo in healing endoscopically-diagnosed erosive esophagitis and in relieving associated heartburn. The erosive esophagitis healing rates were as follows:

EROSIVE ESOPHAGITIS PATIENT HEALING RATES

	Healed/Evaluable			
	Placebo* n = 229		Ranitidine 150 mg q.i.d.* n = 215	
Week 4	43/198	(22%)	96/206	(47%)
Week 8	63/176	(36%)	142/200	(71%)
Week 12	92/159	(58%)	162/192	(84%)

* All patients were permitted p.r.n. antacids for relief of pain.
+ $p<0.001$ versus placebo.

No additional benefit in healing of esophagitis or in relief of heartburn was seen with a ranitidine dose of 300 mg q.i.d.

INDICATIONS AND USAGE: Ranitidine tablets are indicated in:
1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than eight weeks.
2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. No placebo-controlled comparative studies have been carried out for periods of longer than 1 year.
3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of active, benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.
5. Treatment of GERD. Symptomatic relief commonly occurs within 24 hours after starting therapy with ranitidine 150 mg b.i.d.
6. Treatment of endoscopically-diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine 150 mg q.i.d.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

CONTRAINDICATIONS: Ranitidine tablets are contraindicated in patients known to have hypersensitivity to the drug or any of the ingredients (see PRECAUTIONS).

PRECAUTIONS:

General:
1. Symptomatic response to ranitidine therapy does not preclude the presence of gastric malignancy.
2. Since ranitidine is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ranitidine is metabolized in the liver.
3. Rare reports suggest that ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ranitidine therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ranitidine has been reported to bind weakly to cytochrome P-450 *in vitro* recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ranitidine may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life span studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests *(Salmonella, Escherichia coli)* for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ranitidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ranitidine is secreted in human milk. Caution should be exercised when ranitidine is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine. The relationship to ranitidine therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ranitidine administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases of erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypo-

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Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

Studies in dogs receiving dosages of ranitidine in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:

Active Duodenal Ulcer: The current recommended adult oral dosage of ranitidine for duodenal ulcer is 150 mg twice daily. An alternative dosage of 300 mg once daily after the evening meal or at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated (see CLINICAL PHARMACOLOGY, Clinical Trials: *Active Duodenal Ulcer*). Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacid should be given as needed for relief of pain (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Maintenance of Healing of Duodenal Ulcers: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ranitidine 150 mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg four times a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ranitidine, the recommended dosage in patients with a creatinine clearance less than 50 mL/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Ranitidine tablets USP, for oral administration, are supplied as:

150 mg: round, off-white, unscored tablets, film-coated pink, debossed GG 705 on one side and plain on the reverse side, in bottles of 60, 100, 500 and 1000.

300 mg: round, off-white, unscored tablets, film-coated orange, debossed GG 706 on one side and plain on the reverse side, in bottles of 30, 250 and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F). Store in a dry place, and protect from light. Replace cap securely after each opening.

Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

Rev. 97-4M C97/5
7162-6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074467

CHEMISTRY REVIEW(S)

y N

1. CHEMIST'S REVIEW NO. 6

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Patent # 4,128,658 which covers Polymorphic Form I will expire July 25, 1997.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

February 16, 1994--	Original Submission
March 2, 1994--	Telecom Amendment
March 11, 1994--	ANDA New Correspondence
March 21, 1994--	ANDA New Correspondence
November 11, 1994--	ANDA Original Amendment
February 24, 1995-	Bio-New Correspondence
June 8, 1995--	ANDA Original Amendment
October 27, 1995--	New Correspondence-Bio
November 22, 1995--	ANDA Original Amendment
January 22, 1996--	Minor Telecom Amendment
January 30, 1996--	Telephone Amendment
March 13, 1997--	Amendment
April 24, 1997--	Amendment

FDA:

February 23, 1994--	Memo by G. Johnston
March 2, 1994--	Telecom Memo by C. Parise
March 8, 1994--	FTR Memo by G. Johnston
March 8, 1994--	Acknowledgment Receipt
March 21, 1994--	Telecom Memo by C. Parise
June 22, 1994--	Deficiency letter
January 9, 1995--	Bio deficiency letter
March 17, 1995--	Deficiency letter
August 28, 1995--	Labeling review
October 27, 1995--	Deficiency letter
January 22, 1996--	Telecom
January 31, 1996--	TA letter
April 16, 1997--	Chemistry review--acceptable

April 24, 1997-- Labeling review-acceptable
June 1, 1997-- Info letter
July 15, 1997-- Info letter

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs #

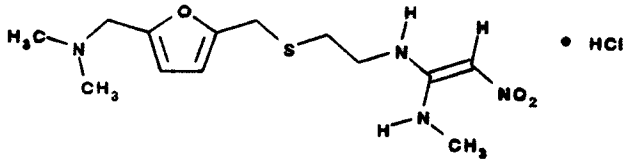
(b)4 - Confidential Business

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg & 300 mg

15. CHEMICAL NAME AND STRUCTURE
Ranitidine Hydrochloride USP

$C_{13}H_{22}N_4O_3S.HCl$; M.W. = 350.87



N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.
CAS [66357-59-3]

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
August 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074467

BIOEQUIVALENCE REVIEW(S)

DEC 9 1994

Ranitidine HCl Tablets
300 & 150 mg
[redacted]
Reviewer: F. Nouravarsani
74467SDW.294

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
February 16, 1994

REVIEW OF A BIOEQUIVALENCE STUDY, DISSOLUTION TESTING AND A WAIVER REQUEST

INTRODUCTION:

Geneva Pharmaceuticals, Inc. has submitted a bioequivalence study and dissolution testing conducted on its test product, Ranitidine Hydrochloride Tablets, 300 mg, and Zantac Tablets, Ranitidine Hydrochloride, 300 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-002) as the listed reference product.

Ranitidine Hydrochloride, a histamine H_2-receptor antagonist inhibits daytime and nocturnal basal gastric acid secretions. It also inhibits the gastric acid secretion stimulated by meal, pentagastrin, and betazole. The oral absolute bioavailability of Zantac is 50%. Mean peak levels of ranitidine are 440 to 545 ng/mL observed at 2 to 3 hours following a 150 mg dose. The administration of food or antacids does not show a significant effect on the absorption of the Zantac. It has been reported in one study that simultaneous administration of Zantac with a high potency antacid (150 m mol) reduced the absorption of Zantac in fasting subjects. The elimination half-life is reported to be 2.5 to 3 hours (PDR 47, 1994).

BIOEQUIVALENCE STUDY:

Objectives:

1. Determine the bioequivalency of the test product, Ranitidine Hydrochloride Tablets, 300 mg and the reference product, Zantac Tablets, 300 mg, under fasting conditions.

2. Compare the in vitro dissolution testing conducted on the test and reference products.

3. Request a waiver of bioequivalence study requirements for Ranitidine Hydrochloride Tablets, 150 mg.

Sponsor: Geneva Pharmaceuticals, Inc., Broomfield, CO
Manufactured by: Geneva Pharmaceuticals, Inc.
Contract Facility: [redacted]

(b)4 - Confidential Business

Study Design:

A single dose of treatment A (test product, lot #6493066, expiration date of September 1995) and treatment B (reference product, lot #Z10203BP, expiration date of February 1995) was administered randomly to healthy volunteers in a two - way crossover study design (protocol/report No. 930825).

Clinical Study Dates:

Phase I: October 8, 1993
Phase II: October 15, 1993
Washout period: 7 days

Subjects:

Twenty six (26) healthy male volunteers were enrolled and completed the study. Subjects number 2, 3, 5, 8, 10, 11, 13, 16, 17, 19, 21, 23, and 25 received treatment A for phase I study. The rest of the volunteers (1, 4, 6, 7, 9, 12, 14, 15, 18, 20, 22, 24, and 26) were dosed treatment A for phase II. The subject age, weight, and height are summarized as following:

Age : 19 - 45 years
Weight: 61.4 - 89.8 kg
Height: 158 - 192 cm

The samples from all 26 subjects were assayed, however statistical data analyses was conducted using subjects 1-24.

Housing, Food and Fluid Intake:

All volunteers were housed in the [redacted] from 12 hours prior to the dose administration until after last blood sample collection at 24 hours. The subjects fasted overnight prior to the dosing until 5 hours after the dosing. The standard meals were served 5 hours and 10 hours after the dose. Water was not allowed from 2 hours before the dose until 5 hours after the dose.

Blood Samples:

Blood samples were collected at predose and after the dose at 0.33, 0.50, 0.67, 1.0, 1.33, 1.5, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours.

Analytical Procedures:

[redacted]

Limit of Quantitation:

The lower limit of quantitation was set at 2.5 ng/mL (the lowest non-zero concentration of a standard sample).

Assay Range: 2.5 - 1000 ng/mL, using Ln polynomial regression.

Statistical Analysis:

The data were analyzed using SAS - GLM procedure. The two one sided t-test procedure (90% confidence intervals) was used to compare the least square means of the parameters of AUC(0-t), AUC(0-Inf), and C(Max) obtained from the test and reference products.

Medical Events:

The reported non-serious, mild, expected drug related medical events are summarized as follows:

Medical Event	Subject #	Product
Headache	16	Test
Dizziness	4	Ref.
Dizziness on standing up	17	Ref.

Results:

The mean serum concentrations of ranitidine are summarized in Table 1. Linear and semi-ln Plots of the mean plasma concentrations of ranitidine versus time for both test and reference products are shown in Figures I and II. The pharmacokinetic parameters are compared in Table 2.

The AUC(0-T) for the test product, 5284.1 hr*ng/mL, is comparable with the AUC(0-T) of 5182.1 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 5323.7 hr*ng/mL, is comparable with the one obtained for the reference product, 5217.7 hr*ng/mL.

The C(Max) for the test product, 1171.0 ng/mL, is comparable with the C(Max) of 1124.9 ng/mL for the reference product.

Mean AUC(0-T)/AUC(0-Inf) ratios for the test and reference products were 99.2% and 99.3%, respectively (Table 3).

Mean test/reference ratios for AUC(0-T), AUC(0-Inf), and C(Max), were 103.7%, 103.7%, and 107.1%, respectively (Table 4).

The 90% confidence intervals for AUC(0-T), AUC(0-Inf), and C(Max) are summarized as follows:

Parameters	Ln-transformed	Un-transformed
AUC(0-T)	94.0 - 109.4	94.3 - 109.6
AUC(0-Inf)	94.1 - 109.5	94.4 - 109.6
C(Max)	91.1 - 114.4	92.1 - 116.1

There are no product, period (p=0.05) and sequence (p=0.1) effects observed for the above pharmacokinetic parametetrs using Ln-transformed or un-transformed parameters.

IN VITRO STUDIES:

Dissolution Testing:

A. Results of the dissolution testing conducted on 12 units of the test product, Ranitidine Tablets, 300 mg (lot #6493066) and the reference product, Zantac Tablets 300 mg (lot #Z10203 BP) are shown in Table 5. Not less than (b)4 (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q - 15% at 45 minutes.

B. Results of the dissolution testing conducted on 12 units of the test product, 150 mg tablets (lot #6493065) and reference product, 150 mg Zantac tablets (lot #Z10773 FP) are shown in Table 5. Not less than (b)4 (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q - 15% at 45 minutes.

Potency:

The assayed potencies of the test products, Ranitidine HCl Tablets, 300 mg, and 150 mg were 98.3% (CV = 0.6, N=6) and 94.5% (CV = 0.4%, N=6) of the labeled amount claimed, respectively. These values fall in the USP required range of 90% - 110%. The assayed potencies of the reference products was reported as 99.2% (CV = 0.8%, N=3)) for the 300 mg tablets, and 96.5% (CV =2.1%, N = 6) for 150 mg tablets.

Content Uniformity:

Values of 100.8% (CV = 1.4%, N=10) and 100.8% (CV = 2.3%, N=10) were obtained as means of percentage of the labeled amount

claimed for 10 Ranitidine HCl Tablets, 300 mg, and 150 mg, respectively. The content uniformities of the reference products were 101.3% (CV = 1.3%, N=10) for 300 mg Tablets, and 101.8% (CV = 1.5%, N=10) for 150 mg Tablets. These values fall in the USP range of 85 - 115% with a CV of NMT 6%.

Waiver Request for Ranitidine HCl Tablets, 150 mg:

The firm requested a waiver of bioequivalence study requirements for its Ranitidine HCl Tablets, 150 mg based on "the similar composition of the products, the satisfactory dissolution profiles for the 150 mg strength, and the fact that an in vivo bioavailability study has been conducted on the 300 mg strength".

COMMENTS:

1. Lots #6493066 (test product) and #Z10203BP (reference product) were used for both the bioequivalence study and the dissolution testing. Theoretical batch size was (b)4 - tablets.

2. The dissolution testings conducted on 300 mg and 150 mg Ranitidine HCl Tablets are acceptable.

3. Application Form FDA 356h was not included in the jacket.

DEFICIENCIES:

1. The samples from all 26 subjects were assayed by error, but the data from 24 subjects were analyzed statistically. The firm should submit the data for all of the subjects, and conduct statistical data analyses using all 26 subjects.

2. Limit Of Quantification (LOQ) was set at 2.5 ng/mL. The firm should be advised to increase the LOQ to a higher value, since significant interference was observed for the following subject samples:

(a) 4-0-2; 9-0-2; 12-0-2; 13-0-1; 14-0-1; 16-0-1; 17-0-1; 24-0-1 (21.2% - 37.1% of the LOQ)

(b) 6-0-1; 9-0-1; 15-0-2; 19-0-2 (48.3% - 59.8% of the LOQ)

(c) 1-0-1; 2-0-2; 13-0-2; 16-0-2; 18-0-2; 19-0-1 (68.2% and 83.1% of the LOQ)

(d) 12-0-1; 23-0-2 (93.6% and 99.0% of the LOQ).

3. All original values together with reassayed, values which

were used in the study, reason for reassaying, and rationale for the used values should be reported, summarized in a table.

For example the original values for the following samples should be reported:

samples 2-0-1; 2-1.5-1; 2-1.67-1; 2-1-2; 2-2.5-2; 10-1.5-1; 13-1.5-1; and 19-2.5-1 were coded as NR (Not Reportable), because there was no sample available for reanalysis due to several prior analysis, or

samples 1-0-2; 1-0.33-2; 6-0.5-2; 12-0-2; 14-0-1; 14-0-2; 15-0-1; 16-16-1; 16-24-1; 18-0-1; 20-0-1; 20-16-2; 21-2-1; 22-0-2; 23-0-1; 23-8-1; 24-0.33-1; and 24-8-2, were reported NR, because difference between values of original and single repeat were greater than 30%.

4. The waiver request for bioequivalence study requirements for 150 mg Ranitidine HCl Tablets may not be granted, since the bio-study conducted on 300 mg Tablets has been found incomplete.

5. It was stated that samples will be stored frozen until 5/25/94, then they will be discarded. The samples were stored less than one year, since the clinical study was started on October 8, 1993. The firm should be informed for the future studies that the storage period should be increased to at least one year.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, comparing it to Zantac Tablets, 300 mg has been found incomplete by the Division of Bioequivalence.

2. The dissolution testings conducted by the Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, and Ranitidine HCl Tablets, 150 mg, lot #6493065 are acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP XXII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the DEFICIENCIES and the RECOMMENDATIONS.

(b)4 - Confidential Business

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE (b)4 - Confidential
FT INITIALED RMHATRE Business

Concur: (b)4 - Confidential Business Date: 12/9/94
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

FNouravarsani/11-30-94/74467SDW.294

CC: ANDA #74-467 (Original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD 658 (Mhatre, Nouravarsani), Drug File, Division File.

Table 1:

Mean (CV%) Serum Concentrations (ng/mL) of Ranitidine, N=24:

Time, hr	Test Product		Reference Product	
0.00	0.000	(--)	0.000	(--)
0.33	158.4	(96)	108.8	(69)
0.50	322.9	(63)	292.9	(52)
0.67	414.5	(47)	386.7	(43)
1.00	600.3	(50)	510.2	(41)
1.33	746.0	(71)	607.5	(50)
1.50	721.2	(61)	682.1	(52)
1.67	686.9	(61)	692.5	(54)
2.00	811.0	(56)	747.9	(60)
2.50	880.1	(50)	751.4	(53)
3.00	836.7	(40)	834.4	(36)
3.50	751.0	(38)	772.7	(41)
4.00	668.1	(33)	694.3	(35)
5.00	549.6	(28)	560.2	(32)
6.00	399.1	(30)	410.0	(28)
8.00	250.5	(28)	244.8	(25)
10.00	134.5	(29)	142.0	(26)
12.00	72.1	(30)	73.8	(26)
16.00	29.3	(37)	29.7	(31)
24.00	7.7	(40)	7.5	(40)

Table 2:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters Obtained for 300 mg Tablets of the Test and Reference Products, N=24:

Parameters	Test Product		Reference Product	
AUC(0-T) hr*ng/mL	5284.1	(24.5)	5182.1	(23.2)
AUC(0-Inf) hr*ng/mL	5323.7	(24.2)	5217.7	(23.0)
C(Max) ng/mL	1171.0	(41.8)	1124.9	(38.3)
T(Max) hr	2.527	(34.1)	2.417	(35.5)
K(Elm) 1/hr	0.223	(14.9)	0.222	(11.1)
T(1/2) hr	3.17	(14.6)	3.16	(12.1)

Table 3: AUC(0-T)/AUC(0-Inf) Percentage

Subject	Test	Reference
01	99.4	99.3
02	98.7	99.6
03	99.5	99.5
04	99.7	99.5
05	99.3	98.3
06	99.6	99.7
07	99.6	99.5
08	99.5	99.7
09	99.3	99.6
10	99.5	99.5
11	99.6	99.6
12	99.6	99.5
13	98.5	98.8
14	98.6	99.0
15	98.8	98.1
16	97.0	99.6
17	99.4	99.3
18	99.1	99.4
19	99.6	99.5
20	99.6	99.5
21	98.8	98.9
22	99.5	99.4
23	98.5	98.8
24	99.6	99.2
Mean%	99.2	99.3
CV%	0.6	0.4
Range%	97.0% - 99.7%	98.1% - 99.7%

Table 4: Ratio Analysis of the Parameters

Subject	(Test/Reference) Percentage AUC(0-T)	AUC(0-Inf)	C(Max)
01	128.2	128.0	156.2
02	87.5	88.3	72.5
03	91.8	91.9	116.6
04	160.3	160.1	152.7
05	85.4	84.5	118.8
06	96.8	96.9	104.2
07	124.9	124.8	146.0
08	95.5	95.7	66.5
09	91.9	92.1	83.5
10	113.1	113.1	201.0
11	128.9	128.9	109.9
12	115.7	115.6	89.1
13	91.2	91.5	83.4
14	93.4	93.7	117.5
15	109.9	109.1	89.5
16	93.1	95.6	129.0
17	88.9	88.9	91.1
18	77.2	77.5	48.8
19	153.6	153.5	145.4
20	61.3	61.3	82.1
21	99.6	99.7	74.4
22	108.5	108.4	105.4
23	88.3	88.5	88.8
24	102.8	102.4	98.6
Mean%	103.7	103.7	107.1
CV%	22.0	21.9	32.3
Range%	61.3-160.3	61.3-160.1	48.8-201.0

Table 5:

Drug (Generic Name):Ranitidine HCl Tablets, USP
Dose Strength: 300 mg, 150 mg
ANDA: #74-467m: Geneva Pharmaceuticals, Inc
Submission Date: February 16, 1994

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: Water at 37° C Volume: 900 mL

Reference Drug, (Manuf.) Zantac, (Glaxo)

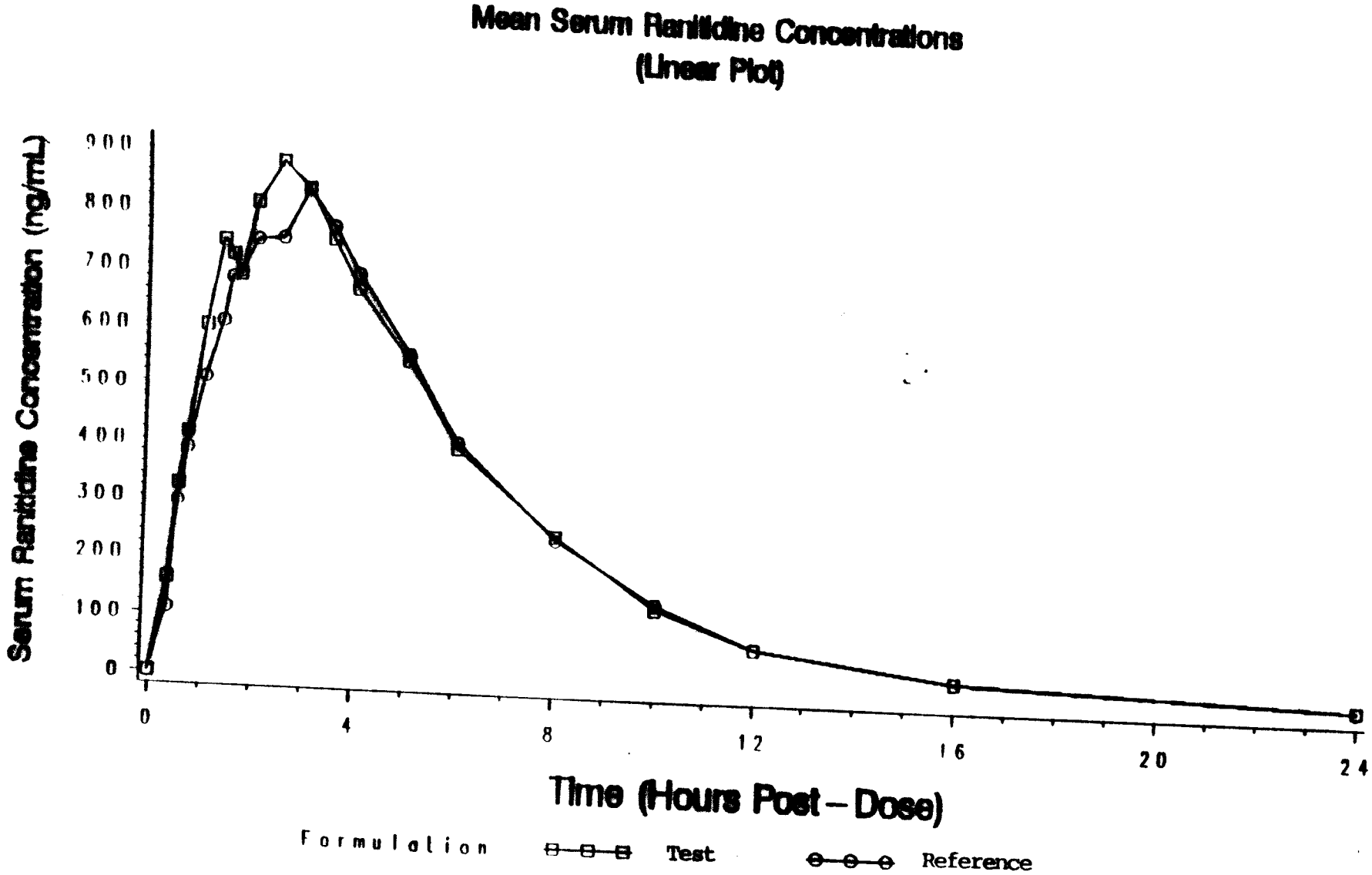
Assay Methodology: (b)4 - Confidential Business

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot # 6493066			Reference Product Lot # Z10203BP		
Minutes	Strength (mg) 300			Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	88.0	(b)4 - Confidential Business	(08.8)	70.0	(b)4 - Confidential Business	(11.7)
30	100.0		(01.8)	93.0		(04.4)
45	100.0		(01.9)	97.0		(02.5)
60	101.0		(01.7)	99.0		(01.9)

Sampling Times	Test Product Lot # 6493065			Reference Product Lot # Z10773FP		
Minutes	Strength (mg) 150			Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	84.0	(b)4 - Confidential Business	(13.1)	41.0	(b)4 - Confidential Business	(12.4)
30	98.0		(01.6)	72.0		(06.0)
45	99.0		(01.6)	89.0		(07.5)
60	99.0		(01.7)	94.0		(04.1)

Figure I


Mean Serum Ranitidine Concentrations
(Linear Plot)
Serum Ranitidine Concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (Hours Post – Dose)
Formulation
Test
Reference

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #74-467 **SPONSOR:** Geneva Pharmaceuticals
Drug: Ranitidine HCl
DOSAGE FORM: Tablets
STRENGTH: 300 mg
TYPE OF STUDY: Single/Fasting
CLINICAL SITE:
ANALYTICAL SIT (b)4 - Confidential Business

STUDY SUMMARY:

Twenty-six (26) healthy male volunteers participated and completed the study. Blood samples were collected from 0.0 - 24.0 hours. Serum levels of ranitidine were measured using (b)4 - method. The 90% confidence intervals calculated for the Ln-transformed parameters of AUC (0-T), AUC(0-Inf), and C(max) fall in the acceptable range of 80% - 125%. The bioequivalence study conducted under fasting conditions has been found acceptable by the Division of Bioequivalence.

DISSOLUTION:

The dissolution testing conducted on 12 units of the test and reference products are acceptable. Not Less Than (b)4 Q) of the labeled amount was dissolved in 45 minutes

PRIMARY REVIEWER: F. Nouravarsani **BRANCH:** III
SIGNITURE: (b)4 - Confidential Business **DATE:** 12/19/95

BRANCH CHIEF: R. Mhatre **BRANCH:** III
SIGNITURE: (b)4 - Confidential Business **DATE:** 12/19/95

DIRECTOR: K. Chan
DIVISION OF BIOEQUIVALENCE:
SIGNITURE: (b)4 - Confidential **DATE:** 1/31/96

DIRECTOR:
OFFICE OF GENERIC DRUGS:

SIGNITURE: _____ **DATE:** _____

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #74-467 **SPONSOR:** Geneva Pharmaceuticals
DRUG: Ranitidine HCl
DOSAGE FORM: Tablets
STRENGTH: 150 mg
TYPE OF STUDY: Dissolution Testing, Waiver Request

DISSOLUTION TESTING SUMMARY:

The dissolution testing conducted on 12 units of the test product, and 12 units of the reference product are acceptable. Not Less Than (b)4(Q) of the labeled amount was dissolved in 45 minutes.

WAIVER OF BIOEQUIVALENCE STUDY:

Waiver of bioequivalence study requirements for 150 mg Ranitidine HCl Tablets, USP may be granted according to 21 CFR, 320.22 (d)(2) based on the following:

(a) Acceptable single-dose bioequivalence study conducted under fasting conditions on the higher strength of Ranitidine HCl Tablets, USP, 300 mg, and Zantac Tablets, 300 mg.

(b) Acceptable dissolution testing conducted on Ranitidine HCl Tablets, 300 and 150 mg, and Zantac Tablets, 300 and 150 mg.

(c) The similarity between the formulations of Ranitidine HCl Tablets, USP, 300 mg and 150 mg.

PRIMARY REVIEWER: F. Nouravarsani **BRANCH:** III

SIGNITURE (b)4 - Confidential Business **DATE:** 12/19/95

BRANCH CHIEF: R. Mhatre **BRANCH:** III

SIGNITURE: (b)4 - Confidential Business **DATE:** 12/19/95

DIRECTOR: K. Chan
DIVISION OF BIOEQUIVALENCE:

SIGNITURE: (b)4 - Confidential **DATE:** 1/31/96

DIRECTOR:
OFFICE OF GENERIC DRUGS:

SIGNITURE: _____ **DATE:** _____

Ranitidine HCl Tablets
USP, 300 & 150 mg
ANDA #74-467
Reviewer: F. Nouravarsani
74467ADW.295

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
February 24, 1995
October 27, 1995

REVIEW OF BIOEQUIVALENCE STUDY AMENDMENTS, DISSOLUTION TESTING AND A WAIVER REQUEST

INTRODUCTION:

Geneva Pharmaceuticals, Inc. has responded to the Division of Bioequivalence deficiency letter dated January 09, 1995.

The firm had submitted a fasting bioequivalence study and dissolution testing conducted on its test product, Ranitidine Hydrochloride Tablets, 300 mg, and Zantac Tablets, Ranitidine Hydrochloride, 300 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-002) as the listed reference product.

Deficiency #1:

The samples from all 26 subjects were assayed by error, but the data from 24 subjects were analyzed statistically. The firm was requested to submit the data for all of the subjects, and conduct statistical data analyses using all 26 subjects.

Response to Deficiency #1:

The data were reanalyzed statistically to include subjects #25 and #26. The pharmacokinetic parameters are compared in Table 1.

The AUC(0-T) for the test product, 5176.6 hr*ng/mL, is comparable with the AUC(0-T) of 5166.8 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 5218.0 hr*ng/mL, is comparable with the one obtained for the reference product, 5203.8 hr*ng/mL.

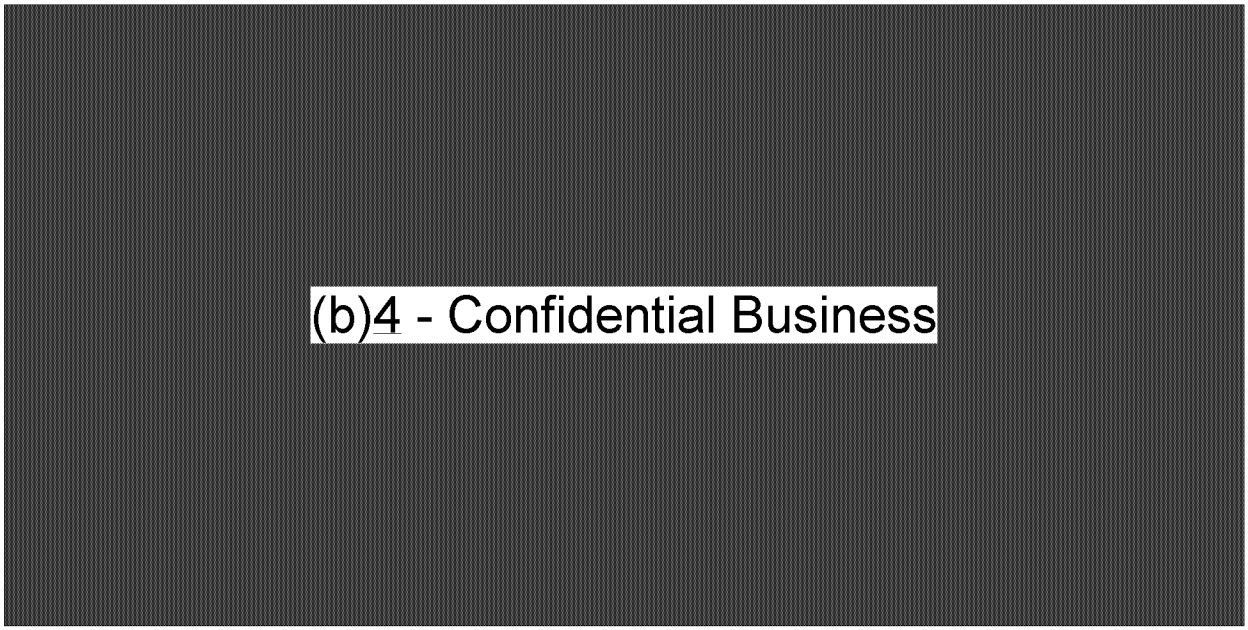
The C(Max) for the test product, 1124.4 ng/mL, is comparable with the C(Max) of 1109.2 ng/mL for the reference product.

Results of the GLM statistical data analyses were not included in the submission dated February 24, 1995. This information was submitted on October 27, 1995 in response to phone call by Dr. Jason Gross. There are no product, period ($p=0.05$) and sequence ($p=0.1$) effects observed for the pharmacokinetic parametetrs using Ln-transformed or un-transformed parameters.

The 90% confidence intervals for ln-transformed parameters, AUC(0-T), AUC(0-Inf), and C(Max) fall in the required range by the Division of Bioequivalence (summarized in Table 1).

No errors were found by spot checking of the calculations and statistical data analysis.

Samples from subjects #25 and #26 were assayed with runs BWE 18 and BWE 19, respectively. The accuracy and precision for the Standard and Quality Control Samples including all runs are summarized as follows:



Reviewer Comment:

The firm's response is acceptable.

Deficiency #2:

Limit Of Quantification (LOQ) was set at 2.5 ng/mL. The firm was advised to increase the LOQ to a higher value, since significant interferences were observed for the following subject samples:

(a) 4-0-2; 9-0-2; 12-0-2; 13-0-1; 14-0-1; 16-0-1; 17-0-1; 24-0-1 (21.2% - 37.1% of the LOQ)

(b) 6-0-1; 9-0-1; 15-0-2; 19-0-2 (48.3% - 59.8% of the LOQ)

(c) 1-0-1; 2-0-2; 13-0-2; 16-0-2; 18-0-2; 19-0-1 (68.2% and 83.1% of the LOQ)

(d) 12-0-1; 23-0-2 (93.6% and 99.0% of the LOQ).

Response to Deficiency #2:

(b)4 - Confidential has stated that a higher LOQ will be set for ranitidine studies in the future. However, Cmax values were higher than 400 times the LOQ. Therefore, the bioequivalence study should not be effected by this interference.

Reviewer Comment:

The response is acceptable for this study.

Deficiency #3:

The firm was requested to report all original values together with reassayed, values which were used in the study, reason for reassaying, and rationale for the used values summarized in a table.

Response to Deficiency #3:

The firm had not submitted the original or reassayed values for all of the reanalyzed samples in its amendment dated February 24, 1995. These information were requested by phone call of Dr. Jason Gross. The values for all of the reassayed samples were submitted in the current amendment (submition date: October 27, 1995).

Reviewer Comment:

The response is acceptable.

Deficiency #4:

The waiver request for bioequivalence study requirements for 150 mg Ranitidine HCl Tablets was not granted, since the bio-study conducted on 300 mg Tablets was found incomplete.

Response to Deficiency #4:

The firm has resubmitted its request for waiver of bioequivalence study requirements for Ranitidine Tablets, 150 mg based on:

a. the bioequivalence study conducted on the 300 mg strength,

b. the comparative dissolution testing conducted on 300 mg and 150 mg of the test and reference products (Table 2), and

c. the similar composition of the products (Table 3).

The results of the in vitro studies are summarized as follows:

Dissolution Testing:

A. Results of the dissolution testing conducted on 12 units of the test product, Ranitidine Tablets, 300 mg (lot #6493066) and the reference product, Zantac Tablets 300 mg (lot #Z10203 BP) are shown in Table 2. Not less than (b)4 (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q - 15% at 45 minutes.

B. Results of the dissolution testing conducted on 12 units of the test product, 150 mg tablets (lot #6493065) and reference product, 150 mg Zantac tablets (lot #Z10773 FP) are shown in Table 2. Not less than (b)4 (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q - 15% at 45 minutes.

Potency:

The assayed potencies of the test products, Ranitidine HCl Tablets, 300 mg, and 150 mg were 98.3% (CV = 0.6, N=6) and 94.5% (CV = 0.4%, N=6) of the labeled amount claimed, respectively. These values fall in the USP required range of 90% - 110%. The assayed potencies of the reference products was reported as 99.2% (CV = 0.8%, N=3)) for the 300 mg tablets, and 96.5% (CV =2.1%, N = 6) for 150 mg tablets.

Content Uniformity:

Values of 100.8% (CV = 1.4%, N=10) and 100.8% (CV = 2.3%, N=10) were obtained as means of percentage of the labeled amount claimed for 10 Ranitidine HCl Tablets, 300 mg, and 150 mg, respectively. The content uniformities of the reference products were 101.3% (CV = 1.3%, N=10) for 300 mg Tablets, and 101.8% (CV = 1.5%, N=10) for 150 mg Tablets. These values fall in the USP range of 85 - 115% with a CV of NMT 6%.

Reviewer Comment:

The waiver of bioequivalence study requirements for Ranitidine Tablets, 150 mg may be granted.

Deficiency #5:

It was stated that study samples will be stored frozen until 5/25/94, then they will be discarded. The samples were stored less than one year, since the clinical study was started on October 8, 1993. The firm was informed that the storage period should be increased to at least one year for the future studies.

Response to Deficiency #5:

The firm responded that: "The samples continue to remain in storage at [redacted] The statement in the analytical report was incorrect and should indicate that the samples will remain in storage until 25May94 at which time the client will be contacted regarding further retention of stored samples."

Reviewer Comment:

The firm's response is acceptable.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, comparing it to Zantac Tablets, 300 mg, lot #Z10203BP manufactured by Glaxo Pharmaceuticals has been found acceptable by the Division of Bioequivalence.

2. The dissolution testings conducted by the Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, and Ranitidine HCl Tablets, 150 mg, lot #6493065 are acceptable.

3. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalence and in-vitro dissolution testing.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

5. Waiver of bioequivalence study requirements may be granted for the firm's Ranitidine HCl Tablets, 150 mg.

(b)4 - Confidential Business

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE (b)4 - Confidential Business 12/18/95
FT INITIALED RMHATRE

Concur: (b)4 - Confidential Date: 12/18/95
for Keith Chan, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/12-08-95/74467ADW.295

CC: ANDA #74-467 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD 658 (Mhatre, Nouravarsani), Drug File, Division File.

Table 1:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters, and 90% CI (ln-transformed) Obtained for 300 mg Tablets of the Test and Reference Products, N=26:

Parameter	Test	Reference	90% CI (ln-trans.)
AUC(0-T) hr*ng/mL	5176.6(25)	5166.8(22)	92.1% - 107.0%
AUC(0-Inf) hr*ng/mL	5218.0(25)	5203.8(22)	92.3% - 107.1%
C(Max) ng/mL	1124.4(44)	1109.2(38)	87.5% - 110.2%
T(Max) hr	2.602 (33)	2.500 (35)	
K(Elm) 1/hr	0.2205(16)	0.2201(11)	
T(1/2) hr	3.219 (16)	3.192 (12)	

Table 2:

Drug (Generic Name):Ranitidine HCl Tablets, USP
Dose Strength: 300 mg, 150 mg
ANDA: #74-467: Geneva Pharmaceuticals, Inc
Submission Date: February 24, 1995

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: Water at 37° C Volume: 900 mL

Reference Drug, (Manuf.) Zantac, (Glaxo)

Assay Methodolog (b)4 - Confidential Business

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot # 6493066			Reference Product Lot # Z10203BP		
Minutes	Strength (mg) 300			Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	88.0	(b)4 - Confidential Business	(08.8)	70.0	(b)4 - Confidential Business	(11.7)
30	100.0		(01.8)	93.0		(04.4)
45	100.0		(01.9)	97.0		(02.5)
60	101.0		(01.7)	99.0		(01.9)

Sampling Times	Test Product Lot # 6493065			Reference Product Lot # Z10773FP		
Minutes	Strength (mg) 150			Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	84.0	(b)4 - Confidential Business	(13.1)	41.0	(b)4 - Confidential Business	(12.4)
30	98.0		(01.6)	72.0		(06.0)
45	99.0		(01.6)	89.0		(07.5)
60	99.0		(01.7)	94.0		(04.1)

Table 3:

Formulation Comparison:

Ingredients	150 mg Tablet	300 mg Tablet
Ranitidine HCl, USP	167.395 mg(a)	334.790 mg(b)
Microcrystalline Cellulose, NF	[redacted]	
Hydroxypropyl Methylcellulose [redacted] USP		
Sodium Starch Glycolate, NF		
[redacted] Alcohol		
Magnesium Stearate, NF		
Opadry Pink [redacted]		
Opadry Orang[redacted]		
Opadry Clear [redacted]		
Purified Water		

(b)4 - Confidential Business

(a) Equivalent to 150 mg ranitidine base.

(b) Equivalent to 300 mg ranitidine base.

FIRM: **Geneva Pharmaceuticals, Inc.** ANDA: **74-467**
DRUG: **Ranitidine Tablets USP, 150 mg and 300 mg**

LABELING OF THE LISTED DRUG

FIRM: Glaxo Pharmaceuticals and the Labeling Guidance for Ranitidine Tablets USP, Rev. 11/93 NDA# 18-703
APPROVAL DATE: March 29, 1995 REV.DATE: March 1995

CONTAINER LABELS

APPROVED COPY ON FILE? **No**
USP CONTAINER/CLOSURE REQUIREMENTS: **Preserve in a tight, light-resistant container. No temperature recommendations.**
RECOMMENDED STORAGE STATEMENT:
ANDA: **Store at CRT. Store in a dry place, and protect from light. Dispense in a tight, light-resistant container.**
NDA: **Store between 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening.**
OTHER KEY ISSUES: **The June 8, 1995 submission contains container labels for the 1000s container size. In the previous submission the firm had submitted container labels for package sizes of 30's, 100's and 500's (150 mg) and 30's, 250's (300 mg). The firm stated the 1000s are the only package size they intend to distribute.(See page 6 in June 8, 1995 Amendment)**

INSERT LABELING

PATENT & EXCLUSIVITY ISSUES: a. The patent for Form I, patent (4128658), expires on July 25, 1997 (This has been extended by GATT from December 5, 1995). Due to this extension the insert labeling needs to be updated to include the indication for Alternative Dosage of 300 mg once daily after the evening meal . Form II, patent (4521431), expires on June 4, 2002.

b. Patent # 5028432 is a patent for the gelatin capsule formulation entitled Pharmaceutical capsules containing ranitidine . This patent expires on July 2, 2008. Patent 4880636 expires on May 13, 2008. Patent 4585790 expires May 11, 2004 (extended by GATT from 4/29/2003) and patent 5102665 expires June 23, 2009 (extended by GATT from 4/7/2009).

c. Exclusivity for I-75 (Treatment of Endoscopically Diagnosed Erosive Esophagitis) expires on May 19, 1995.

d. Exclusivity for D-21 (Alternative Dosage of 300 mg once daily after the evening meal) expires on February 28, 1997.

e. Exclusivity for I-116 (Maintenance of Healing of Erosive Esophagitis) expires on November 3, 1997.

f. Because the exclusivity for Form 1 expires on July 25, 1997, the indication for Alternative Dosage of 300 mg daily after the evening meal will now be included in the labeling. The indications for Maintenance of Healing of Erosive Esophagitis and Maintenance Therapy for Gastric Ulcer

not be contained in the insert labeling of this ANDA because they expire post July 25, 1997.

BIO ISSUES: **Pending.**

ALL INACTIVE INGREDIENTS CITED? **Yes**
OTHER KEY ISSUES:

APPROVAL SUMMARY

CONTAINER LABELS: **1000s (150 mg and 300 mg) - June 8, 1995**

CARTON LABELING (SUBMISSION DATE): None

INSERT LABELING: **November 22, 1995 (Rev. 95-11M)**

FORMULATION/SCORING SUMMARY: **Same as the NDA. Both the 150 mg and 300 mg tablets are NOT scored. The firm revised the shape of the 300 mg tablet to be round.**

COMMENTS OR FUTURE REVISIONS NEEDED: **CONTRAINDICATIONS - Insert (see PRECAUTIONS) at the end of the sentence.**

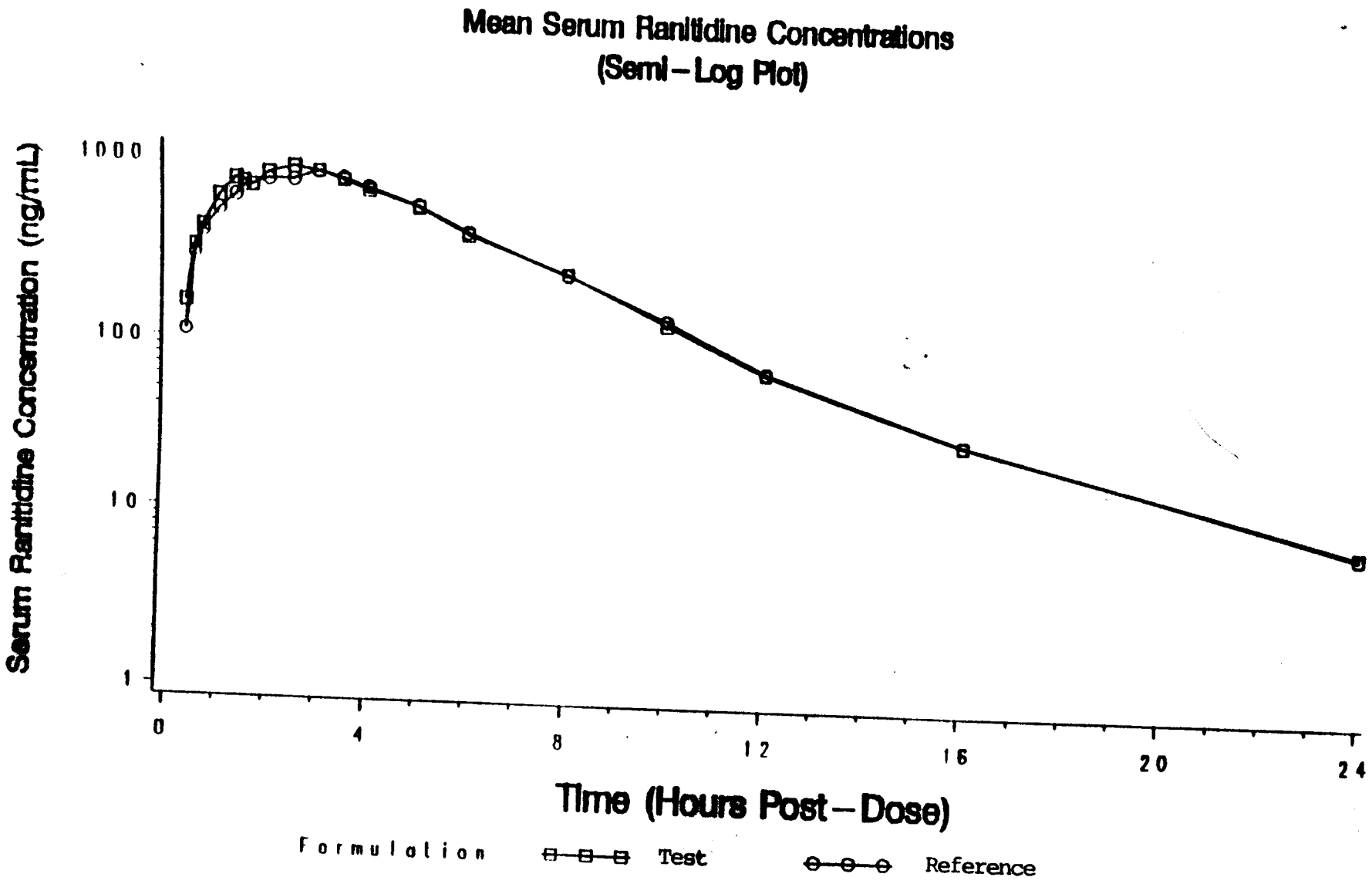
1° REVIEWER: /S/

2° REVIEWER:

SUPERVISOR: /S/

DATE: 11/29/95

Figure II


Mean Serum Ranitidine Concentrations
(Semi-Log Plot)
Serum Ranitidine Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (Hours Post-Dose)
Formulation
Test
Reference